-- 227. A recombinant vector comprising a DNA regulatory element operably linked to a DNA molecule encoding the cystic fibrosis transmembrane conductance regulator protein of Table 1, wherein the DNA molecule is capable of stable propagation in *E. coli* as a result of:

(*a*) said DNA regulatory element permitting maintenance of the DNA molecule in *E. coli* at a low copy number, or

(*b*) said nucleotide sequence of the DNA molecule being modified to disrupt its expression in *E. coli* while allowing its expression in mammalian cells. --

Cancel claims 202-225.

REMARKS

The attention of the Patent & Trademark Office is directed to the fact that claims 226 and 227 are believed to define the same patentable invention under 37 CFR §1.601(n) as claims 1-16 of United States Patent No. 5,240,846 issued to Francis S. Collins and James M. Wilson, assignors to The Regents of the University of Michigan.

Claims 226 and 227 have been presented for purposes of interference with United States Patent No. 5,240,846 (hereinafter "the '846 Patent"). As is documented below, Applicants are entitled under 35 USC §120 to an effective date of March 5, 1990 (for Serial No. 07/488,307) whereas the '846 Patent is entitled to an effective date of September 18, 1990 (for Serial No. 07/584,275). Consequently the present request is governed by 37 CFR §1.607.

1. Background of the Interfering Invention

The commonly disclosed invention is based on the isolation of a DNA molecule which encodes the cystic fibrosis transmembrane conductance regulator protein (CFTR). As acknowledged in the '846 Patent at col. 7, lines 59 *et seq.*, prior attempts to reconstitute a full length CFTR cDNA from overlapping clones were unsuccessful. As theorized in the '846 Patent, the proposed root of these problems was that prokaryotic transcription from the CFTR cDNA sequence resulted in expression of a protein toxic to the prokaryotic cell.

The problem then was to attain stable propagation of the CFTR cDNA in bacteria, notably *E. coli*, while allowing its expression in mammalian cells. Once these problems were identified and solved, the introduction of the DNA into conventional vectors, either for protein production or for gene therapy, presented no problem beyond the skill of the art. The solution disclosed in the '846 Patent involved modifying the nucleotide sequence of the cDNA molecule to disrupt expression in *E. coli,* specifically the introduction of three silent mutations.

Applicants similarly and independently determined that use of prokaryotes led to cell death. Applicants taught one method of solving this problem, namely modification of the nucleotide sequence of the cDNA molecule to disrupt its expression in *E. coli* but not in eukaryotic cells. One such method disclosed by Applicants involved introduction of a single silent mutation.

However, that was not the only possible solution.[1] Applicants taught that the problem could be solved not only by modifying the nucleotide sequence to disrupt expression in prokaryotic cells, through either silent mutations (as mentioned in the '846 Patent) or

[1] The '846 Patent asserted without further elucidation that any method, which through introduction of a silent mutation rendered the "fortuitous *E. coli* promoter" non-functional, could be used (see col. 11, lines 45 *et seq.*).

introduction of an intron, but also through use of a recombinant vector which permitted maintenance of the DNA molecule at a low copy number.

Consequently, both the Patentees and Applicants encountered the same problem. The Patentees arrived at one solution; Applicants arrived at a broader resolution, presenting the art with two possible solutions: (i) use of a DNA regulatory element which permits maintenance of the DNA molecule in *E. coli* at a low copy number, or (ii) modifying the nucleotide sequence of the DNA molecule, thereby disrupting its expression in *E. coli* while allowing its expression in mammalian cells. Two variations of the second of these were disclosed, one involving a point mutation (and thus encompassing the same solution disclosed in the '846 Patent), and the other involving the use of a synthetic intron. Both of these variations were designed to achieve the same result, namely disrupting expression in *E. coli* cells.

2. The Proposed Count

Pursuant to §1.607(2), the following single count is proposed:

> A recombinant vector for a target cell, the vector comprising:
>
> a) a DNA regulatory element; and
>
> b) a normal cystic fibrosis transmembrane regulator gene operably linked to the DNA regulatory element and capable when so linked of expression in the target cell *in vivo* or *in vitro*.

As will be seen, the single count which has been drafted is broader than the patent claims corresponding thereto; *i.e.*, in accordance with §1.606 the proposed count is not narrower in scope than the patent claim designated to correspond to it. Thus while claim 1 of the '846 Patent is limited to a recombinant *viral* vector for expression of the normal CFTR gene in the target cell (and thus limits the regulatory mechanism of that vector to at least a portion of a viral genome), the count extends to any recombinant vector, viral or otherwise, for a target cell in which the vector has (*i*) a DNA regulatory element and (*ii*) a

normal CFTR gene operably linked to the regulatory element for expression in the target cell.

Moreover, the language of the patent claim concerning the intended use of the vector has been omitted as being immaterial. As the Examiner noted in Paper No. 39 in the present application, the recitation of an intended function such as "for treating" or "capable of" do not constitute a patentable or material limitation. *See, e.g., In re Thuau*, 135 F.2d 344, 57 USPQ 324 (CCPA 1943); *In re Pearson*, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974); *In re Tuominen*, 671 F.2d 1359, 213 USPQ 89 (CCPA 1982); *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 780, 782, 227 USPQ 773, 777-78 (Fed. Cir. 1985); and *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1655 (Fed. Cir. 1990).

3. The Claims of the '846 Patent Corresponding to the Count

Claim 1 of the '846 Patent, the broadest claim asserted, reads as follows:

> A recombinant viral vector for treating a defect in the gene for cystic fibrosis transmembrane regulator in target cell, the vector comprising:
>
> a) the DNA of or corresponding to at least a portion of the genome of a virus which portion is cable [*sic,* capable]of infecting the target cells; and
>
> b) a normal cystic fibrosis transmembrane regulator gene operatively linked to the DNA and capable of expression in the target cell in vivo or in vitro.

Pursuant to §1.607(3), claim 1 of the '846 Patent would correspond to the count.

In addition, all of claims 2-16 of the '846 Patent are dependent on claim 1, directly or indirectly. Since under §1.606 any single patent claim designated to correspond to the count (here claim 1) is initially presumed not to contain separate patentable inventions and since under 35 USC §112, 2nd¶, all of claims 2-16 necessarily incorporate all of the limi-

tations of claim 1 (upon which they depend), claims 2-16 also would correspond to the single count subject to a motion under §1.633(c).

4. Applicants' Claims Corresponding to the Count

As noted, the following two claims would correspond to the count:

> 226. A recombinant vector comprising a DNA regulatory element operably linked to a DNA molecule that encodes a wild-type, human cystic fibrosis transmembrane conductance regulator protein, wherein the DNA molecule is capable of stable propagation in *E. coli*.
>
> 227. A recombinant vector comprising a DNA regulatory element operably linked to a DNA molecule encoding the cystic fibrosis transmembrane conductance regulator protein of Table 1, wherein the DNA molecule is capable of stable propagation in *E. coli* as a result of:
>
> (*a*) said DNA regulatory element permitting maintenance of the DNA molecule in *E. coli* at a low copy number, or
>
> (*b*) said nucleotide sequence of the DNA molecule being modified to disrupt its expression in *E. coli* while allowing its expression in mammalian cells.

As in the case of claim 1 of the '846 Patent, claim 227 is directed to recombinant vectors and closely follows previous claim 225 which was allowable (as indicated by the Examiner in the Interview Summary Record of July 21, 1996). Claim 227 has been changed only in that the term "recombinant vector" has been used in place of "plasmid".

With respect to the requirements of §1.607(4), the claims of the patent and those of the application corresponding to the proposed count do not correspond exactly to the proposed count, but each defines the same patentable invention.[2] The count thus is a "phantom count", as authorized by §1.601(f), in that it is broader in scope than all claims which correspond to it. As is clear from the Examiner's previous rejection of Applicants'

[2] Under §1.601(f), a claim that is identical to the count is said to "correspond exactly" to the count whereas a claim which is not identical to the count is said to "correspond substantially" to the count.

claims over the '846 Patent, the criterion of §1.601(n) has been satisfied in that Applicants' invention is the "same patentable invention" as the invention of the '846 Patent since Applicants' invention is the same as (35 USC §102) or is obvious (35 USC §103) in view of the invention claimed in the '846 Patent, *assuming* the invention of the '846 Patent were prior art with respect to Applicants' invention.

The use of a broader phantom count is permissible where a party's best proofs lie outside the scope of a narrower count limited to the patent claim. MPEP §2309.01; *Wheelock v, Wolinski*, 175 USPQ 216 (Comm'r Pats. 1963); *Morehouse v. Armbruster*, 183 USPQ 182 (Bd. Pat. Intf. 1973); *Nelson v. Drabek*, 212 USPQ 98 (Comm'r Pats. 1979). That is the case with Applicants' proofs.

That both the claims of the '846 patent and Applicants' claims correspond to the proposed count is shown by the Correspondence Table below.

CORRESPONDENCE TABLE

'846 CLAIM 1	PROPOSED COUNT	APPLICANTS' CLAIM 226	APPLICANTS' CLAIM 227
A recombinant viral vector for treating a defect in the gene for cystic fibrosis transmembrane regulator in target cell, the vector comprising:	A recombinant vector for a target cell, the vector comprising:	A recombinant vector comprising:	A recombinant vector comprising:
a) the DNA of or corresponding to at least a portion of the genome of a virus which portion is cable [sic, capable] of infecting the target cells; and	a) a DNA regulatory element and	a DNA regulatory element	a DNA regulatory element
b) a normal cystic fibrosis transmembrane regulator gene operatively linked to the DNA and capable of expression in the target cell in vivo or in vitro	b) a normal cystic fibrosis transmembrane regulator gene operably linked to the DNA regulatory element and capable when so linked of expression in the target cell *in vivo* or *in vitro*	operably liked to a DNA molecule that encodes a wild-type, human CFTR protein, wherein the DNA molecule is capable of stable propagation in *E. coli*.	operably linked to a DNA molecule encoding the cystic fibrosis Trans-membrane conductance regulator protein of Table 1, wherein the DNA molecule is capable of stable propagation in *E. coli* as a result of: (a) said DNA regulatory element permitting main-tenance of the DNA molecule in *E.* coli at a low copy number, or (b) said nucleotide sequence of the DNA molecule being modified to disrupt its expression in *E. coli* while allowing its expression in mammalian cells.

5. Application of the Terms of Applicants' Claims

There follows an analysis of the support for claims 226 and 227, found not only in the present case but also in Applicants' benefit application, Serial No. 07/488,307 filed March 5, 1990. As is clear from that analysis, claims 226 and 227 are fully supported by the disclosure of each application.

SUPPORT TABLE		
CLAIM	**S/N 07/488,307**	**S/N 08/807,132**
226. A recombinant vector comprising a DNA regulatory element operably linked to a	Page 3, line 22-28: The most preferred embodiments of the present invention include cDNA's coding for the entire CFTR protein coding sequence of 4440 nucleotides and advantageously include regulatory sequences from the flanking regions of the cDNA, such as the ribosome binding site located immediately upstream of the initiator methionine of the CFTR open reading frame (Kozak, Nucleic Acids Res. 12, 857 (1984); Kozak Cell 44, 283 (1986)).	Page 4, line 25-29: Preferred embodiments of the present invention include cDNA's coding for the entire CFTR protein coding sequence of 4440 nucleotides and advantageously include regulatory sequences from the flanking regions of the cDNA, such as the ribosome binding site located immediately upstream of the initiator methionine of the CFTR open reading frame (Kozak, 1984; Kozak, 1986).
DNA molecule that encodes a wild-type, human cystic fibrosis transmembrane conductance regulator protein,	Table 1 Page 1, lines 6-12: This invention relates to the use of recombinant DNA techniques to produce a single DNA sequence coding for the entire amino acid sequence of the cystic fibrosis transmembrane conductance regulator (CFTR), and in particular it relates to the use of low copy number plasmids and introns to allow stable maintenance of CFTR coding sequences in host cells including E. coli.	Table 1 Page 6, lines 7-9: Table 1 shows the sequence of that portion of CFTR cDNA encoding the complete CFTR protein within plasmid pSC-CFTR2 including the amino acid sequence of the CFTR open reading frame;

SUPPORT TABLE

CLAIM	S/N 07/488,307	S/N 08/807,132
	Page 4, lines 31-33: Table 1 shows the sequence of that portion of CFTR cDNA encoding the complete CFTR protein within plasmid pSC-CFTR2 including the amino acid sequence of the CFTR open reading frame;	
wherein the DNA molecule is capable of stable propagation in *E. coli*.	Page 3, lines 9-12: In accordance with the principles and aspects of the present invention there are provided recombinant DNA molecules encoding CFTR including most preferred cDNA molecules which can be stably propagated in host E. coli cells.	Page 4, lines 11-15: In accordance with the principles and aspects of the present invention there are provided recombinant DNA molecules encoding CFTR including most preferred cDNA molecules which can be stably propagated in host E. coli cells and which can be used to transform mammalian cells resulting in expression of CFTR.
227. A recombinant vector comprising a DNA regulatory element operably linked to a DNA molecule encoding the cystic fibrosis transmembrane conductance regulator protein of Table 1,	Page 3, line 22-28: The most preferred embodiments of the present invention include cDNA's coding for the entire CFTR protein coding sequence of 4440 nucleotides and advantageously include regulatory sequences from the flanking regions of the cDNA, such as the ribosome binding site located immediately upstream of the initiator methionine of the CFTR open reading frame (Kozak, Nucleic Acids Res. 12, 857 (1984); Kozak Cell 44, 283 (1986)).	Page 4, line 25-29: Preferred embodiments of the present invention include cDNA's coding for the entire CFTR protein coding sequence of 4440 nucleotides and advantageously include regulatory sequences from the flanking regions of the cDNA, such as the ribosome binding site located immediately upstream of the initiator methionine of the CFTR open reading frame (Kozak, 1984; Kozak, 1986)...
wherein the DNA molecule is capable of stable propagation in *E. coli* as a result of:	Page 3, lines 9-12: In accordance with the principles and aspects of the present invention there are provided recombinant DNA molecules encoding CFTR including most preferred cDNA molecules which can be stably propagated in host E. coli cells.	Page 4, lines 11-15: In accordance with the principles and aspects of the present invention there are provided recombinant DNA molecules encoding CFTR including most preferred cDNA molecules which can be stably propagated in host E. coli cells and which can be used to transform

SUPPORT TABLE

CLAIM	S/N 07/488,307	S/N 08/807,132
		mammalian cells resulting in expression of CFTR.
a) said DNA regulatory element permitting maintenance of the DNA molecule in *E. coli* at a low copy number, or	Page 3, lines 21 - Page 4, line 3: The most preferred embodiments of the present invention include cDNA's coding for the entire CFTR protein coding sequence of 4440 nucleotides and advantageously include regulatory sequences from the flanking regions of the cDNA, such as the ribosome binding site located immediately upstream of the initiator methionine of the CFTR open reading frame (Kozak, Nucleic Acids Res. 12, 857 (1984); Kozak Cell 44, 283 (1986)). These cDNA's are ideally cloned in plasmid vectors containing origins of replication that allow maintenance of recombinant plasmids at low copy number in E. coli cells. These origins of replication may be advantageously selected from those for the E. coli plasmids pMB1 (15-20 copies per cell), p15A (10-12 copies per cell) or pSC101 (approximately 5 copies per cell) or other vectors which are maintained at low copy number (e.g. less than about 25) in E. coli cells (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, New York 1989).	Page 4, line 29 - Page 5, line 3: These cDNA's are ideally cloned in plasmid vectors containing origins of replication that allow maintenance of recombinant plasmids at low copy number in E. coli cells. These origins of replication may be advantageously selected from those for the E. coli plasmids pMB1 (15-20 copies per cell), p15A (10-12 copies per cell) or pSC101 (approximately 5 copies per cell) or other vectors which are maintained at low copy number (e.g. less than about 25) in E. coli cells (Sambrook et al., 1989).
(b) said nucleotide sequence of the DNA molecule being modified to disrupt its expression in *E. coli* while allowing its expression in mammalian cells.	Page 16, lines 15-28: Thus, an additional advantageous procedure for maintaining plasmids containing CFTR cDNAs in E. coli would be to alter the sequence of this potential promoter such that it will not function in E. coli. This may be accomplished without altering the amino acid sequence encoded by the CFTR cDNA. Plasmids containing complete or	Page 15, line 33 - Page 16, line 10: Thus, an additional advantageous procedure for maintaining plasmids containing CFTR cDNAs in E. coli would be to alter the sequence of this potential promoter such that it will not function in E. coli. This may be accomplished without altering the amino acid sequence encoded by the CFTR cDNA. More, specifically, plasmids

SUPPORT TABLE

CLAIM	S/N 07/488,307	S/N 08/807,132
	partial CFTR cDNA's would be altered by site-directed mutagenesis using synthetic oligonucleotides (Zoller and Smith, Methods Enzymol. 100, 468, 1983). Specifically, altering the nucleotide sequence at position 748 from a T to C and at position 774 from an A to a G would effectively eliminate the activity of this promoter sequence without altering the amino acid coding potential of the CFTR open reading frame. Other potential regulatory signals within the CFTR cDNA for transcription and translation could also be altered and/or deleted by the same method.	containing complete or partial CFTR cDNA's would be altered by site-directed mutagenesis using synthetic oligonucleotides (Zoller and Smith, Methods Enzymol. 100, 468, 1983). Specifically, altering the nucleotide sequence at position 748 from a T to C and at position 774 from an A to a G effectively eliminates the activity of this promoter sequence without altering the amino acid coding potential of the CFTR open reading frame. Other potential regulatory signals within the CFTR cDNA for transcription and translation could also be advantageously altered and/or deleted by the same method.
	Page 3, lines 15-20: In addition, there are provided recombinant cDNA molecules containing at least one intervening sequence within the CFTR coding sequence. Such a sequence advantageously disrupts expression of protein from the CFTR cDNA in E. coli cells, but allows expression in mammalian cells since such cells are capable of removing the intervening sequence from the initial CFTR RNA transcript.	Page 4, lines 18-22: In addition, there are provided recombinant cDNA molecules containing at least one intervening sequence within the CFTR coding sequence. Such a sequence advantageously disrupts expression of protein from the CFTR cDNA in E. coli cells, but allows expression in mammalian cells since such cells are capable of removing the intervening sequence from the initial CFTR RNA transcript.
	Page 4, lines 5-13: Also described herein are preferred CFTR cDNAs containing a synthetic intron of 83 base pairs between nucleotide positions 1716 and 1717 of the CFTR cDNA sequence, which acts to stabilize the cDNA by disrupting the translational reading frame of the CFTR protein such that neither full length protein nor extensive polypeptide sequences can be synthesized in cells unable to splice mRNA. This allows replication in prokaryotic cells of the CFTR	Page 5, lines 5-12: Also described herein are CFTR cDNAs containing a synthetic intron of 83 base pairs between nucleotide positions 1716 and 1717 of the CFTR cDNA sequence, which acts to stabilize the cDNA by disrupting the translational reading frame of the CFTR protein such that neither full length protein nor extensive polypeptide sequences can be synthesized in cells unable to splice mRNA. This allows replication in (but not CFTR expression) prokaryotic cells of the

SUPPORT TABLE		
CLAIM	**S/N 07/488,307**	**S/N 08/807,132**
	cDNA for subsequent transformation of eukaryotic host cells, most preferably mammalian cells, for subsequent expression. See also Page 13, lines 28-31.	CFTR cDNA for subsequent transformation of eukaryotic host cells, most preferably mammalian cells, for subsequent CFTR expression. See also Page 13, lines 29-31.

6. Effective Dates of the Present Application and the '846 Patent

A. The Applicable Law:

It is fundamental that in order for an earlier application to constitute a constructive reduction to practice, it must satisfy the written ***description*** requirement of 35 USC §112 for the invention claimed in the ***later*** application. *Eiselstein v. Frank*, 52 F.3d 1035, 34 USPQ2d 1467 (Fed. Cir. 1995); *Weil v. Fritz*, 572 F.2d 856, 196 USPQ 600 (CCPA 1978); *In re Scheiber*, 587 F.2d 59, 199 USPQ 782 (CCPA 1978); *In re Gosteli et al.*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989); *Kawai v. Metlesic*, 480 F.2d 880, 178 USPQ 158 (CCPA 1973); *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); and *In re Smyth*, 189 F.2d 982, 90 USPQ 106 (CCPA 1951). Hence to secure the benefit of a prior application under 35 USC §120, that earlier application must support the claims asserted in the later case claiming rights under the statute.

B. The '846 Patent Is Not Entitled to Any Date Prior to September 18, 1990:

Serial No. 07/584,275 (which became the '846 Patent) is asserted to be a CIP of Serial No. 07/401,609; however it is noted that significant material concerning bacterial toxicity resulting from full-length cDNA was added when the CIP was filed. As already noted, the Patentees have candidly admitted in the '846 Patent that early attempts to reconstitute full-length CFTR cDNA from overlapping clones were ***un***successful, that prokaryotic transcription from internal CFTR cDNA sequences resulted in cell death, and that not until

their three silent mutations had been effected were they able to overcome this problem. This being the case, the earlier applications could not have provided a description of the invention which would have enabled one to make and use the subject matter claimed in the '846 Patent. The issue is not whether one skilled in the art might have found a way to overcome these problems, the issue is whether the claimed subject matter is ***described*** in accordance with 35 USC §112. Thus it was not until the Patentees arrived at and disclosed the silent mutation modification that a description of the invention which would have enabled one to make and use the subject matter claimed in the '846 Patent was disclosed. This was not before September 18, 1990.

C. Applicants Are Entitled to An Effective Date of March 5, 1990 for Serial No. 07/488,307:

The same law discussed above applies to Applicants. In contrast to the earlier cases claimed in the '846 Patent, however, Applicants' Serial No. 07/488,307 filed March 5, 1990 disclosed not only the problem (toxicity in *E. coli* cells) but no less than three solutions to that problem: low copy number, introduction of an intron, and point mutation. This is documented in the analysis discussed above. As Applicants have documented, present claims 226 and 227 are fully supported under 35 USC §112 by the disclosure of Serial No. 07/488,307 and thus fully entitled to its date under 35 USC §120. *See Eiselstein v. Frank, supra*; *Weil v. Fritz, supra*; *In re Scheiber, supra*; *In re Gosteli et al., supra*; *Kawai v. Metlesic, supra*; *In re Wertheim, supra*; and *In re Smyth, supra*.

7. The '846 Patent Is Prior Art to Applicants Under 35 USC §102(g) But It Is Not Prior Art Under §102(e) or §103:

As demonstrated above, the '846 Patent is not entitled to the benefit of any earlier application under 35 USC §120. Where a rejection under §102(e) is based upon a patent claiming the benefit of an earlier application, the date of the reference is not that of the earlier application ***unless*** the application discloses, in accordance with §112, the invention

claimed in the patent. *In re Wertheim*, 646 F.2d 527, 209 USPQ 554 (CCPA 1970). The CCPA thus noted:

> Thus, the determinative question here is whether the invention *claimed* in the Pfluger patent finds a *supporting disclosure* in compliance with §112, as required by §120, in the [earlier] application so as to entitle that invention in the Pfluger patent, as "prior art" to the filing date of Pfluger I. *Without such support, the invention cannot be regarded as prior art as of that filing date.* 646 F.2d 527, 209 USPQ 554 [emphasis added].

In order to be "prior art" under §102(e), the reference in *Wertheim* (the Pfluger patent) required the benefit of a prior application's filing date. However, the CCPA found that the claims in the *patent* were not supported under 35 USC §112 by the disclosure of the earlier filed *application*. Consequently, the patent was not a reference under 35 USC §102(e) or §103. *Wertheim,* 209 USPQ at 566.

In short, where a patent is not entitled to the benefit of an earlier application under 35 USC §120 because the earlier application does not disclose the invention claimed in the patent in accordance with 35 USC §112 , the patent is a 35 USC §102(e) reference only as of ***its*** filing date, ***not*** the filing date of the parent application.

In order for the '846 Patent to be an effective §102(e) reference therefore against the claims of the present application, the *claims* of the '846 Patent must, under *Wertheim*, find 35 USC §112 support in an earlier application. S*ee also Ex parte Ebata*, 19 USPQ2d 1952 (Bd. Pat. App. Intf. 1991). This includes compliance with the description and enablement requirements. *See In re Scheiber, supra*; *In re Gosteli, supra*; and *Ex parte Marhold*, 231 USPQ 904 (Bd. App. 1984). Since the claims of the '846 Patent clearly do not find such support (recall the Patentees admitted they could ***not*** reconstitute a full length CFTR cDNA from overlapping clones and thus could not have achieved any vector), clearly the effective date of the '846 Patent is September 18, 1990.

The Examiner has repeatedly asserted that the '846 Patent is "prior art" as against Applicants. As demonstrated herein, however, Applicants are entitled to an effective date of March 5, 1990 for Serial No. 07/488,307. Thus Applicants present claims are fully supported by the disclosure of Serial No. 07/488,307.

Applicants concede that issuance of a patent to them is improper until the issue arising under section (g) of 35 USC §102 is resolved. That is why an interference is being provoked. Applicants respectfully submit, however, that the '846 Patent is not prior art under 35 USC §102(e) or §103.

Consider for example the consequences were Applicant to submit a declaration under 37 CFR §1.131, as they are prepared to do. The '846 Patent can be easily "removed" even without reliance by Applicants on Serial No. 07/488,307's filing date of March 5, 1990. Yet the '846 Patent cannot be removed in this fashion if it claims the same patentable invention as defined by §1.601(n). *See* 37 CFR §1.131 and MPEP §715.

Because there is a conflict between Applicant's and Collins' *claims*, and not a conflict between the parties' *disclosures*, the '846 Patent is prior art to Applicants under 35 USC §102(**g**); it is ***not*** prior art, however, under §102(e) or §103.

8. Applicants Complied with 35 USC §135(b)

The '846 Patent issued on August 31, 1993. Although claim 226 and 227 are newly presented, there clearly has been compliance with 35 USC §135(b). Thus it has been consistently held that under the statute, it is not necessary that the interference be provoked within one year or even that patent claims be copied within one year; it is required only that *substantially* the same subject matter has been claimed by the applicant prior to expiration of one year from the issuance of the patent. *See, e.g., Stalego v. Hetmes*, 263 F.2d 334, 120 USPQ 473 (CCPA 1959); *Olin v. Duerr*, 175 USPQ 707 (Bd. Pat. Intf.

1972); *Loewenstein v. Terasawa*, 177 USPQ 84 (Bd. Pat. Intf. 1972); *Wetmore v. Miller*, 477 F.2d 960, 177 USPQ 699 (CCPA 1973); and *Ex parte Fine*, 217 USPQ 76 (Bd. App. 1981). Such compliance can be demonstrated even with now-canceled claims. *Corbett v. Chisholm*, 568 F.2d 759, 196 USPQ 337 (CCPA 1977).

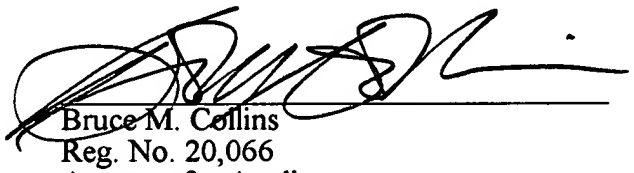
When this case was filed on July 2, 1993, prior to issuance of the '846 Patent, original claim 1 was directed to a DNA sequence coding cystic fibrosis transmembrane conductance regulator; claim 13, added on October 26, 1993, claimed a low copy vector whereas claim 15, added at the same time, claimed a vector in which the DNA had an intron within the cystic fibrosis transmembrane conductance regulator encoding region. All of this was claimed prior to August 31, 1994. That such subject was substantially the same as the '846 Patent also is evidenced by the Examiner's rejection under 35 USC §102(e) based on the '846 Patent (See Paper No. 12 mailed November 23, 1993); *i.e.*, the Examiner recognized that Applicants in fact were claiming the same subject matter.

CONCLUSION

For the foregoing reasons, it is submitted an interference should be promptly declared between claims 226 and 227 of the present application and claims 1-16 of United States Patent No. 5,240,846 and such action is earnestly solicited. A summary of the relevant PTO 850 form information is annexed for the convenience of the Examiner.

Applicants believe no fee is due in connection with this Supplemental Amendment. However, should a fee be deemed due, authority is hereby given to charge same to Deposit Account 13-2165.

Respectfully submitted,



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PTO 850 INFORMATION

NAME	SERIAL NO.	FILING DATE	PATENT NO.
Collins *et al.*	**07/584,275**	**September 18, 1990**	**5,240,846**
Claims corresponding to this count: **1-16**		Claims not corresponding to this count: **None**	
Accorded the benefit of:			
COUNTRY	SERIAL NO.	FILING DATE	PATENT NO.
None			

NAME	SERIAL NO.	FILING DATE	PATENT NO.
Gregory *et al.*	**08/807,132**	**July 2, 1993**	**None**
Claims corresponding to this count: **226, 227**		Claims not corresponding to this count: **None**	
Accorded the benefit of:			
COUNTRY	SERIAL NO.	FILING DATE	PATENT NO.
United States	**07/613,592**	**November 15, 1990**	**None**
United States	**07/589,295**	**September 27, 1990**	**None**
United States	**07/488,307**	**March 5, 1990**	**None**

COUNT **1** OF **1** COUNT

A recombinant vector for a target cell, the vector comprising:

a) a DNA regulatory element; and

b) a normal cystic fibrosis transmembrane regulator gene operably linked to the DNA regulatory element and capable when so linked of expression in the target cell *in vivo* or *in vitro*.